THE REMARKS

The Amendments

Prior to entering the amendments, Claims 1 and 3-15 are pending. Claims 2 and 16-21 are withdrawn.

Applicants apologize to the Examiner that many minor amendments are made in the specification. Most of the amendments merely correct obvious typographical or grammatical errors. The amendments are necessary to present the application in a correct manner.

Claim 3 is amended to recite a dinucleotide compound of Formula I, or salts thereof. Support for the amendment can be found at page 3, line 31.

Claim 3 is amended to correct the structure of Formula IV to delete the H on position N9 and add a bond, which correctly shows a purine residue, linked through the 9-position. Formula V is amended to add a bond on N1 position to correctly show a pyrimidine residue, linked through the 1-position.

Claim 3 is amended to recite that D_1 and D_2= O or CH_2; support for the amendment can be found at page 6, line 18 and page 9, line 21. Claim 3 is also amended to recite that B and B' are independently a purine or a pyrimidine residue. Support for the amendment can be found at page 12, line 31. Claim 3 is further amended to recite R_3 and R_4; support for the amendment can be found at page 9, line 27.

Claim 6 is amended to clarify the meaning of the claim.

Claim 4, 5, 8, and 13 are amended to correct the parent claim number.

New Claim 22 is supported by Claim 20.

New Claim 23 is supported by Claim 21.

New Claim 24 further limits Claim 3.

New Claim 25 further limits Claim 24 and is supported by the specification at page 14, lines 13-27.

No new matter is added to any of the above amendments. The Examiner is requested to enter the amendments and reconsider the application.

Objection to the Specification

The Abstract of the Disclosure is objected to because of the use of the word "novel" to describe the compositions of the invention. Applicants have amended the Abstract to delete the word "novel."

Double Patenting Rejection

1. Provisional rejection under under 35 U.S.C. §101

Claims 1, 4, 5, and 13 are provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 3, 5, 16, and 6 of copending Application No. 09/643,138.

Claim 1 is canceled. Claims 4, 5 and 13 are amended to depend on Claim 3, in which the $P2Y_{12}$ receptor antagonist compound is a dinucleotide compound of Formula I. Therefore, Claims 4, 5 and 13 of the instant application are not the same as those in the copending Application No. 09/643,138.

2. Provisional obviousness-type double patenting rejection

Claims 3, 6-12, and 14-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 4, 16, 26, 30-34, 7-15, and 11 of copending Application No. 09/643,138.

Applicant will address this provisional rejection when the instant claims are otherwise allowable.

35 U.S.C. §103 Rejections

Claims 1 and 3-15 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Yerxa, *et al.*, U.S. Patent No. 6,323,187 (Yerxa); Kim, *et al.*, *Journal of Biological Chemistry* (19934), Vol. 269, pages 647i1-6477 (Kim); and Markaldn, et al., U.D. Patent No. 5,814,609 (Markland).

1. **Yerxa, *et al.***

The present invention is directed to a method of preventing or treating diseases or conditions associated with platelet aggregation by administering to a subject a pharmaceutical

composition comprising a therapeutic effective amount of $P2Y_{12}$ receptor **antagonist** compound, which is a dinucleotide compound of Formula I.

Yerxa, *et al.* disclose P^1-(cytidine 5')-P^4-(uridine 5'-)tetraphosphate, an **agonist** of $P2Y_2$ and/or $P2Y_4$ purinergic receptors. Yerxa, *et al.* also disclose methods of enhancing secretion clearance and enhancing ciliary beat frequency in a mammal using P^1-(cytidine 5')-P^4-(uridine 5'-)tetraphosphate.

(a) $P2Y_{12}$ antagonists vs. $P2Y_2$ and/or $P2Y_4$ agonists

Yerxa, *et al.* disclose compounds that are **agonists** of the $P2Y_2$ and/or $P2Y_4$ purinergic receptor. Yerxa, *et al.* do not teach or suggest $P2Y_{12}$ receptor **antagonist**.

Binding of ADP to platelet receptors is required for elicitation of the ADP-induced platelet responses. There are at least three P2 receptors expressed in human platelets: a cation channel receptor $P2X_1$, a G protein-coupled receptor $P2Y_1$, and a G protein-coupled receptor $P2Y_{12}$ (also referred to as $P2Y_{ac}$ and $P2_T$). The $P2X_1$ receptor is responsible for rapid calcium influx and is activated by ATP and by ADP. However, its direct role in the process of platelet aggregation is unclear. The $P2Y_1$ receptor is responsible for calcium mobilization, shape change and the initiation of aggregation. $P2Y_{12}$ receptor is responsible for inhibition of adenylyl cyclase and is required for full aggregation. (See specification at page 2, line 31 through page 3, line 7)

The compounds used in the present methods are functionally different from those disclosed in Yerxa, *et al.* in that the present compounds are **antagonists** of $P2Y_{12}$ receptors, whereas the Yerxa compounds are **agonists** of $P2Y_2$ and/or $P2Y_4$ purinergic receptors.

(b) Difference in Chemical Structures

The dinucleotide compounds used in the present methods are structurally different from those disclosed in Yerxa, *et al.* in that:

Y'= H, OH, or OR_1,

Z'= H, OH or OR_2,

with the proviso that at least one of Y', and Z', is OR_1 or OR_2, (instant Claim 3)

With the above proviso, one of Y' and Z'is an ether, ester, thioester, carbamate, thiocarbamate, cyclical acetal, cyclical ketal, or cyclical orthoester. Yerxa, *et al.* disclose P^1-

(cytidine 5')-P^4-(uridine 5'-)tetraphosphates where Y, Y', Z and Z' all equal to OH. Yerxa, *et al.* do not teach or suggest the compounds used in the present invention.

(c) Difference in Diseases Treated.

Yerxa, *et al.* disclose methods of enhancing secretion clearance and enhancing ciliary beat frequency in a mammal. Yerxa, *et al.* also disclose methods of treating sinusitis, otitis media, dry eye disease, and retinal detachment. Yerxa, *et al.* do not teach or suggest a method of preventing or treating diseases or conditions associated with platelet aggregation.

Because Yerxa, *et al.* do not teach or suggest (a) an antagonist of $P2Y_{12}$ receptors, (b) the claimed compounds, or (c) the diseases treated by the instant methods, the present claims are not obvious over Yerxa, *et al.*

2. Kim, *et al.*

(a) Kim, *et al.* do not disclose dinucleotide compounds.

Kim, *et al.* disclose some mononucleotide purinergic receptors such as adenosine 5'-O-(1-thiotriphosphate), ATP, adenosine 5'-O-(3-thiotriphosphate), 3'-O-(4-benzoyl-benzoyl)ATP, α,β- and β,γ-methylene ATP. Kim, *et al.* do not teach or suggest any dinucleotide compound.

(b) Kim, *et al.* do not teach or suggest using $P2Y_{12}$ receptor antagonist to treat platelet aggregation.

The purpose of Kim, *et al.* is to describe "a purinergic P2 receptor on PC12 cells that does not fit the classification for the P_2x, P_2y, P_2t, P_2u, P_2z receptor subtypes." (See Abstract last sentence)

Platelet aggregation is only mentioned in the reference at page 6471, first paragraph under the Abstract:

> Extracellular nucleotides can influence many biological functions, including platelet aggregation, vascular tone, cell division, cardiac and skeletal muscle contraction, as well as peripheral and central neurotransmission (1). These extracellular actions of ATP are mediated through purinergic receptors that have been classified by Burnstock (2) as P2 receptors."

The above paragraph only discloses that ATP (an extracellular mononucleotide) can influence platelet aggregation. Throughout the reference, there is no teaching or suggestion that a $P2Y_{12}$ receptor antagonist can be used to treat platelet aggregation.

3. U.S. Patent 5,814,609 (Markland, *et al.*)

Markland, *et al.* do not disclose purinergic receptors or dinucleotide compounds.

Even with hindsight construction, the combination of Yerxa, *et al.*, Kim, *et al.* and Markland, *et al.* do not produced Claims 3-15. Therefore, the 35 U.S.C. §103(a) rejection of Claims 3-15 should be withdrawn.

CONCLUSION

Applicants believe that the application is in good and proper condition for allowance. Early notification of allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned.

Respectfully submitted,

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